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**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**
**BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES**

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| Applicant: | David A. Cheresh *et al.* | ) | |
| Serial No. | 09/538,248 | ) | |
| Filed: | March 29, 2000 | ) | Art Unit: 1652 |
| For: | METHODS USEFUL FOR TREATING VASCULAR LEAKAGE AND EDEMA USING SRC OR YES TYROSINE KINASE INHIBITORS | ) | Atty Docket No.: TSRI 651.3 |
| Examiner: | Rebecca Prouty, Ph.D. | ) | |

**BRIEF ON APPEAL**

Mail Stop Appeal Briefs - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This is an appeal from the final rejection of claims 1-4 and 16-20, in the above-identified application. This brief is submitted in triplicate and is accompanied by a check #23715 in the amount of $320, to cover the fee required under 37 CFR §1.17(c).

**1. Real Party in Interest**

This application is assigned to The Scripps Research Institute, licensed to Merck KGaA, Darmstadt, Germany, and sublicensed to Targegen, Inc.

**2. Related Appeals and Interferences**

There are no related appeals or interferences.

**3. Status of All Claims**

Claims 1-4, inclusive, and 16-20, inclusive, are on appeal. Claims 3, 4, 19, and 20 were amended during prosecution. The claims on appeal are set forth in Appendix I hereto for ready reference. Claims 5-15, inclusive, and 21-31, inclusive, have been withdrawn from consideration as being drawn to non-elected subject matter.

**4. Status of All Amendments Filed Subsequent to Final Rejection**

The response filed on March 11, 2003, subsequent to the final rejection, has been entered by the Examiner.

**5. Concise Summary of the Invention**

The invention provides methods and articles of manufacture suitable for inhibiting vascular permeability increases in diseased, inflamed or traumatized tissue. Tissue damage related to associated vascular leakage and edema is ameliorated. Vascular permeability is often associated with increased levels of vascular endothelial growth factor (VEGF) in a tissue, and can lead to swelling of and damage to the affected tissue. VEGF is a regulator of both vascular permeability (i.e., the degree of plasma fluid leakage through the blood vessel wall) and of blood vessel formation (i.e., angiogenesis). Surprisingly, the methods and articles of manufacture of the present invention selectively inhibit VEGF-induced vascular permeability without adversely affecting other VEGF-induced responses that can be beneficial to recovery from injury, such as angiogenesis.

A method aspect of the invention involves contacting a swollen (i.e. edematous) tissue with a vascular permeability modulating amount of an inhibitor of a Src family tyrosine kinase. Preferably the inhibitor is a chemical (i.e., non-proteinaceous) inhibitor such as pyrazolopyrimidine PP1, pyrazolopyrimidine PP2, PD173955, AGL1872, PD162531, Radicol R2146, or Geldanamycin.

The articles of manufacture of the present invention comprise a packaged pharmaceutical composition that includes a Src family tyrosine kinase inhibitor in a pharmaceutically acceptable carrier. The pharmaceutical composition is capable of modulating vascular permeability increase in a tissue suffering from a disease condition. The package includes a label which indicates that the pharmaceutical composition can be used for treatment of vascular leakage or edema associated disease conditions.

**6. Concise Statement of All Issues Presented for Review**

The following issues are presented for review:

I. Whether claims 1-4, inclusive, and 16-20, inclusive, would have been obvious under 35 U.S.C. 103(a) from the teachings of any one of van Bruggen *et al.*, Aiello *et al.* or Jirousek *et al.* in view of Munshi *et al.*

II. Whether claims 1-4, inclusive, and 16-20, inclusive, would have been obvious under 35 U.S.C. 103(a) from the teachings of any one of van Bruggen *et al.*,

Aiello *et al.* or Jirousek *et al.* in view of Hanke *et al.* and either of He *et al.* or Cooke *et al.*

III. Whether claims 1-4, inclusive, and 16-20, inclusive, would have been obvious under 35 U.S.C. 103(a) from the teachings of any one of van Bruggen *et al.*, Aiello *et al.* or Jirousek *et al.* in view of Hanke *et al.* and Eliceiri *et al.* (1998).

**7. Grouping of Claims for Each Ground of Rejection**

The rejected claims do not stand or fall together for any ground of rejection.

Claims 1-4, inclusive, and 16-20, inclusive, have been rejected under 35 U.S.C. 103(a) over three different combinations of references. In particular, the claims stand rejected as unpatentable over:

(a) any one of van Bruggen *et al. J. Clin. Invest.*, 1999; 104(11):1613-1620, Aiello *et al.* U. S. Patent No. 6,284,751 or Jirousek *et al.* U. S. Patent No. 6,093,740 in view of Munshi *et al. J. Immunol.*, 2000; 164:1169-1174;

(b) any one of van Bruggen *et al.*, Aiello *et al.* or Jirousek *et al.* in view of Hanke *et al.*, *J. Biol. Chem.*, 1996; 271(2):695-701 and either of He *et al., J. Biol. Chem.*, 1999; 274(35):25130-25135 or Cooke *et al.*, *FASEB J.*, 2000; 14(4):A145; and

(c) any one of van Bruggen *et al.*, Aiello *et al.* or Jirousek *et al.* in view of Hanke *et al.* and Eliceiri *et al. Mol. Biol of the Cell*, 1998; 9(Supp.):2444.

Independent claim 1 defines a method for ameliorating tissue damage related to vascular leakage or edema comprising contacting the tissue with a vascular permeability modulating amount of a pharmaceutical composition comprising a Src family tyrosine kinase inhibitor.

Claims 2-4, inclusive, and 16 depend directly or indirectly on claim 1 and include all the limitations thereof.

Claim 2 is specific to the method of claim 1 where the inhibitor is a chemical inhibitor (i.e., non-proteinaceous).

Claim 3 is specific to the method of claim 2 where the chemical inhibitor is pyrazolopyrimidine PP1, pyrazolopyrimidine PP2, PD173955, AGL1872, PD162531, Radicol R2146 or Geldanamycin.

Claim 4 is specific to the method of claim 3 where the chemical inhibitor is pyrazolopyrimidine PP1.

Claim 16 is specific to the method of claim 1 where the inhibitor is a Src tyrosine kinase inhibitor (i.e., an inhibitor of Src - one member of the Src family of tyrosine kinases).

Independent claim 17 defines an article of manufacture comprising packaging material and a pharmaceutical composition contained within the packaging material, wherein the pharmaceutical composition is capable of modulating vascular permeability increase in a tissue suffering from a disease condition. The pharmaceutical composition comprises a Src family tyrosine kinase inhibitor and a pharmaceutically acceptable carrier therefor. The packaging material comprises a label indicating that the pharmaceutical composition can be used for treatment of vascular leakage or edema associated disease conditions.

Claims 18-20, inclusive, depend directly or indirectly on claim 17 and include all of the limitations thereof.

Claim 18 is specific to the article of claim 17 where the Src family tyrosine kinase inhibitor is a chemical inhibitor.

Claim 19 is specific to the article of claim 18 where the chemical inhibitor is pyrazolopyrimidine PP1, pyrazolopyrimidine PP2, PD173955, AGL1872, PD162531, Radicol R2146, or Geldanamycin.

Claim 20 is specific to the article of claim 18 where the chemical inhibitor is pyrazolopyrimidine PP1.

**8. Argument**

**I. Introduction**

The mechanisms and effects of vascular permeability are very complex, involving many interrelated and interdependent cell signaling pathways. The Declaration of Dr. David Cheresh, of record and submitted together with the Applicants' Response Under Rule 116, filed on April 2, 2003, explains the state of the prior art and the significance of the invention. The complexity of the subject warrants a brief background discussion of vascular permeability and of significant aspects of the present invention, however.

Vascular endothelial growth factor (VEGF) is a cell signaling protein involved in a number of physiological events including angiogenesis (formation of new blood cells), endothelial cell proliferation and growth, and vascular permeability. Vascular permeability refers to the fluid barrier properties of blood vessels; i.e., the tendency of serous fluid inside the blood vessel to penetrate through the blood vessel wall and to leak

out into the surrounding tissue. Excessive vascular permeability (vascular leakage) leads to a watery fluid build-up in the tissues surrounding the blood vessel (i.e., edema). The edema associated with vascular leakage can cause tissue damage. Increased vascular permeability is associated with increased levels of VEGF secretion, for example, in ischemic tissues (i.e., tissues with impaired blood flow). VEGF signaling is poorly understood. See He *et al.* at page 25130.

As noted by Dr. Cheresh, Src family tyrosine kinases are involved in numerous growth factor pathways. See Declaration of Cheresh, ¶ 10. The Thomas *et al.* review entitled "Cellular Functions Regulated by Src Family Kinases" lists ten classes of receptor pathways that couple with Src kinases, each of these classes including numerous members. See the Table of Contents of Thomas *et al.*, p. 513-514, and related text. While Src tyrosine kinase activity has been associated with angiogenesis (see Eliceiri *et al.* 1998), there is no report of record linking Src tyrosine kinase activity with vascular permeability prior to the present application and its parent applications.

Yet, as ubiquitous as Src kinases are in their biochemical interactions, it is indeed surprising that Src deficient (knockout) mice develop normal vasculature and survive to adulthood, whereas VEGF knockout mice do not develop normal vasculature and die *in utero*. See Declaration of Cheresh, ¶ 15. Thus, while some connection between VEGF signaling and Src kinase activity was known in the art, it was not evident to one of ordinary skill that Src activity was involved in all aspects of VEGF signaling. In other words, Src inhibition is not the functional equivalent of VEGF inhibition, as seems to be the position of the Examiner. If it were, Src knockout mice would not be expected to develop to adulthood.

Also, it is known that Src family tyrosine kinase is activated *inter alia*, by angiogenesis growth factors bFGF and VEGF, yet VEGF is the only known angiogenesis growth factor that induces vascular permeability. See Declaration of Cheresh, ¶¶ 10 and 11. Besides, there is more than one VEGF signaling pathway. See Declaration of Cheresh, ¶ 8; Dvorak, *et al., American Journal of Pathology*, 146 (5), 1029-1039 (1995). Thus, one of ordinary skill would have had no reason to selectively target Src family tyrosine kinase for inhibition.

Applicants have discovered that inhibitors of Src family tyrosine kinases ameliorate tissue damage due to VEGF-induced vascular permeability but do not inhibit

activation of the VEGF receptor upon binding of VEGF to its receptor. Methods and articles of manufacture embodying this discovery are claimed in the present application. Surprisingly, vascular permeability and attendant tissue damage are inhibited without adversely affecting VEGF-induced effects that are beneficial to recovery from injury, such as angiogenesis. See Specification, page 62, lines 22-30 and the Figures discussed therein. While the present claims have been rejected as being obvious over a number of reference combinations, these rejections are unwarranted, as discussed in detail below, and should be reversed.

**II. Claims 1-4 and 16-20 Would Not Have Been Obvious From the Applied References**

The test for obviousness is what the combined teachings of the references would have suggested to one of ordinary skill tin the art. *In re Young*, 927 F.2d 588, 18 USPQ2d 1089 (Fed. Cir. 1991). In order to establish a *prima facie* case for obviousness, all claim limitations must be taught or suggested by the prior art. *In re Royka*, 180 USPQ 580 (CCPA 1974). Additionally, "All words in a claim must be considered in judging the patentability of that claim against the prior art." *In re Wilson*, 165 USPQ 494, 496 (CCPA 1970). Furthermore, there must be a teaching in the references themselves that would have motivated one of skill in the art at the time the invention was made to combine the references with a reasonable expectation of success. *In re Vaeck*, 947 F.2d 488, 493, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991). That is not the case here. The various combinations of the applied references would not have rendered the present claims obvious to one of ordinary skill in the art at the time the claimed invention was made even if it is assumed, *arguendo*, that the attempted combinations are indeed proper.

In addition, a *prima facie* case of obviousness can be rebutted by showing that the prior art teaches away from the claimed invention in any material respect. *In re Geisler*, 116 F.3d 1465, 1469, 43 USPQ2d 1362, 1365 (Fed. Cir. 1997). Dr. Cheresh in his Declaration at ¶¶ 6 and 13 amply demonstrates that the prior art teaches away from the claimed invention in several material respects as discussed in detail herein below.

**A. Claims 1-4, inclusive, and 16-20, inclusive, would not have been obvious under 35 U.S.C. 103(a) from any one of van Bruggen *et al.*, Aiello *et al.* or Jirousek *et al.* in view of Munshi *et al.***

Claims 1-4, inclusive, and 16-20, inclusive, stand rejected as being obvious under 35 U.S.C. 103(a) over any one of van Bruggen *et al.*, Aiello *et al.* or Jirousek *et al.* in view of Munshi *et al.* This rejection is unwarranted. No suggestion is provided to one of ordinary skill to focus on Src family tyrosine kinase inhibition when seeking to ameliorate tissue damage due to vascular permeability. The cited references also do not provide a valid basis for the attempted combination thereof.

The object of van Bruggen *et al.* is to provide a method of treating ischemia or trauma induced cerebral edema. Van Bruggen *et al.* achieves this goal by administering to mice suffering from brain trauma a truncated Flt-1 receptor (a VEGF receptor) fused to a Fc-IgG (an immunoglobulin). This fusion protein reportedly prevents VEGF signaling by directly binding to and sequestering VEGF. Src family tyrosine kinase is not VEGF, however.

Sequestration of VEGF would necessarily affect all VEGF related physiological manifestations, including those which are beneficial in wound healing such as angiogenesis. In addition, van Bruggen *et al.*, at page 1613, notes that "The role of VEGF in the pathogenesis of stroke and in the formation of cerebral edema is unclear with contradictory experimental observations cited in the literature."

Van Bruggen *et al.* does not teach or suggest any relationship between vascular permeability and Src family tyrosine kinases, nor does it teach or suggest that inhibition of a Src kinase will selectively modulate vascular permeability and ameliorate tissue damage without adversely affecting beneficial VEGF modulated wound healing mechanisms such as angiogenesis, as is surprisingly achieved by the present invention. Significantly, van Bruggen *et al.* does not mention Src kinases at all.

Unlike van Bruggen *et al.*, both Aiello *et al.* and Jirousek *et al.* are directed to a β-isozyme selective PKC inhibitor that counteracts the effects of VEGF, but is <u>not</u> a VEGF inhibitor, thus these two references are even further removed from the claimed subject matter. Aiello *et al.* teach that the "expression of VEGF is controlled by multiple mechanisms" (col. 8, lines 40-41). Jirousek *et al.* teach that VEGF stimulates vascular permeability through activation of the β-isozyme of PKC, and that inhibitors of this

particular enzyme will, therefore, attenuate or inhibit dermal edema. PKC is not a Src family tyrosine kinase, but is a serine/threonine kinase involved in a number of cell signaling pathways. Neither reference teaches or suggests a role for Src family tyrosine kinases in ameliorating tissue damage due to vascular permeability or edema, which is required by the present claims. These references do not mention Src either.

Munshi *et al.* does not cure the aforedescribed defects of the principal references, and is not combinable with the principal references in any event. Munshi *et al.* is directed to reduction of proliferation of Kaposi's Sarcoma (KS) cells, and discloses a relationship between Src family tyrosine kinases and VEGF signaling with respect to cell proliferation. In fact, Munshi *et al.*, like Aiello *et al.*, teach that the VEGF signaling pathways are complex. For example, Munshi *et al.* reports that inhibition of cSrc increases MAP kinase activity (a serine/threonine kinase) but has no effect on Flk-1/KDR, a primary VEGF receptor protein (see Munshi *et al.*, p. 1173, paragraph bridging col. 1 and col. 2). Munshi *et al.* also teaches that reduced KS cell growth in the presence of cSrc inhibitors "is likely due in part to blunted MAP kinase activation." This reference does not teach any relationship between MAP kinase activity and vascular permeability. In fact, Munshi *et al.* does not provide any insight into vascular permeability effects of VEGF, nor does the reference teach or suggest that edema caused by vascular permeability can be reduced by inhibition of Src family tyrosine kinases. There is certainly no suggestion in the references that Src inhibition can selectively reduce vascular permeability without adversely affecting angiogenesis, as is the case with the present invention.

The Examiner has argued (Paper No. 13, pages 3-4) that van Bruggen *et al.*, which teaches inhibition of VEGF with a specific fusion protein as treatment of edema in the mouse brain, renders claim 1 obvious when combined with the teaching of Munshi *et al.* that inhibition of Src with pyrazolopyrimidine PP1 interferes with cellular proliferation. See also Paper No. 18, page 4. There is no valid scientific basis for the attempted combination of these diverse teachings in the first place. Vascular permeability and cellular proliferation are different phenomena. Moreover, the Declaration of Cheresh cites articles by Losordo *et al.*, Hayashi *et al.* and Bao *et al.*, which clearly rebut the Examiner's argument. The Losordo *et al.* article teaches the use of VEGF to therapeutically induce angiogenesis in ischemic tissues. This would have led one of skill in the art away from interfering with VEGF signaling as a treatment for ischemic edema. See Declaration of

Cheresh ¶ 6. Hayashi *et al.* and Bao *et al.* teach that treatment with VEGF reduces edema due to ischemic brain damage. The teachings of Hayashi *et al.* and Bao *et al.* (i.e., reduction of edema by treatment with VEGF), are directly opposite to those of van Bruggen *et al.*, which teaches reduction in edema by sequestering VEGF. Thus, one of skill in the art would not have had a reasonable expectation of success in reducing edema by interrupting just one of the many VEGF related signaling pathways (i.e. inhibiting a Src family tyrosine kinase), since interference with VEGF signaling could have either a beneficial effect (van Bruggen *et al.*) or a detrimental effect (Hayashi *et al.*) on edema. See Declaration of Cheresh, ¶ 13.

To counter the foregoing, the Advisory Action states that the publications relied upon by Dr. Cheresh "teach treatment of ischemia (loss of blood flow) and not vascular edema (excessive accumulation of blood) with VEGF." (Paper No. 18, paragraph bridging pages 2 and 3, emphasis added). The Advisory Action then goes on to state that ischemia and edema are "opposite effects" and that "one would not find the treatment of ischemia with VEGF to teach away from the treatment of vascular edema by inhibiting VEGF signaling." *Id.* These statements are scientifically incorrect. Moreover, these statements reveal a fundamental misunderstanding of what these publications teach to those skilled in the art. Edema and ischemia are not opposite effects. Edema is not "an excessive accumulation of blood." Rather, edema is an accumulation of serous fluid (not blood) in a tissue. See *Dorland's Medical Dictionary* 25th Ed., W. B. Saunders, Philadelphia, pp. 494-95 (1974), attached hereto in Appendix II. An accumulation of blood is generally referred to as a hematoma, and indicates rupture and/or destruction of a blood vessel. See *Dorland's Medical Dictionary* 25th Ed., p. 690, attached hereto in Appendix II. Vascular permeability, on the other hand, is a natural phenomenon. It is not a rupture or destruction of a blood vessel, but a transient reduction in the fluid barrier properties of the blood vessel wall that allows serous fluid (i.e., plasma, not blood) to leak into the surrounding tissue, resulting in edema. See, generally, van Bruggen *et al.* pp. 1613 and 1619. Thus, it appears that an unfortunate misunderstanding of the concepts of edema and vascular permeability has occurred, which has led to an unwarranted rejection of Applicants' argument. As pointed out by Dr. Cheresh, Bao *et al.* teaches (1) that reducing VEGF production or inhibiting VEGF signaling should negatively impact ischemic tissues, and (2)

that this teaching would have discouraged one of ordinary skill from considering interference with VEGF signaling to treat edema. See Declaration of Cheresh, ¶ 9.

In the case on appeal, claim 1 is directed to a method of ameliorating tissue damage related to vascular leakage or edema by contacting tissue with a vascular permeability modulating amount of pharmaceutical composition containing a Src family tyrosine kinase inhibitor. The claimed method is aimed at ameliorating tissue damage by alleviating edema due to vascular permeability, and, as correctly noted in the Advisory Action (Paper No. 18, p. 3), is not limited to treatment of edema due to ischemia. Claim 1 does encompass treatment of edema in ischemic tissue, however. Losordo *et al.*, Hayashi *et al.* and Bao *et al.*, discussed by Dr. Cheresh in his Declaration, would have pointed one of skill in the art away from interfering with VEGF signaling to treat edema in ischemic tissue, since these references clearly contradict van Bruggen *et al.* Therefore, one of skill in the art would not have had a reasonable expectation that an interference with VEGF signaling by inhibiting a Src family tyrosine kinase would beneficially reduce edema and attendant tissue damage.

In fact, the applied references, alone and in combination, do not teach or suggest to one of ordinary skill <u>any</u> relationship whatsoever between Src family tyrosine kinases and vascular permeability. There is certainly no teaching or suggestion in the applied references that would have led one of skill in the art to use a Src family tyrosine kinase inhibitor to reduce vascular permeability with any reasonable expectation of success. The applied references do not teach or suggest limitations of the claim. There is no scientific justification for the attempted combination of references. And, even combined, the references do not establish a *prima facie* case of obviousness. The obviousness rejection clearly is improper.

Even assuming, *arguendo*, that a *prima facie* case has been established, the *prima facie* case has been rebutted. The Losordo, *et al.* article discussed by Dr. Cheresh in his Declaration at ¶ 6 clearly teaches away from any interference with VEGF specifically when treating ischemic edema. The teachings of Hayashi, *et al.* and Bao, *et al.*, are to the same effect. See Cheresh Declaration ¶ 13. The applied references also do not teach or suggest the surprising and unexpected selectivity achieved by the claimed invention for ameliorating tissue damage by modulating vascular permeability, yet without adversely affecting VEGF induced responses that are beneficial to recovery from injury, such as

angiogenesis. (See the data described in the specification at page 62, lines 22-30). The scientific literature as well as the unexpected selectivity of the claimed method effectively rebut any colorable argument that the applied references render claim 1 obvious.

Claim 2 is directly dependent on claim 1 and is specific for a method where the Src family tyrosine kinase inhibitor is a chemical inhibitor (i.e., as opposed to a protein-based inhibitor). Although Munshi *et al.* discloses a chemical inhibitor of Src family tyrosine kinases (PP1), this particular chemical inhibitor is disclosed in a different context, the inhibition of VEGF-induced growth of Kaposi's Sarcoma cells. Besides, PP1 does not inhibit VEGF. See Munshi *et al.*, at p. 1171. Thus, one of ordinary skill would not have been motivated to substitute PP1 for the VEGF sequestering agent of van Brueggen, *et al*, or the ß-isozyme inhibitor of Aiello, *et al.*, and Jirousek, *et al.* The applied references, alone or in combination, do not teach or suggest the necessary connection between Src kinase inhibition and inhibition of vascular permeability, as described above.

Claim 3 is directly dependent on claim 2 and further defines the Src inhibitor as being selected from seven specific chemical inhibitors, including PP1. As noted above, while Munshi *et al.* discloses PP1, the applied references, even if combined for the sake of argument, fail to teach or suggest the necessary connection between Src inhibition and inhibition of vascular permeability by these specific chemical inhibitors.

Claim 4 is directly dependent on claim 3 and further defines the Src inhibitor as PP1. Munshi *et al.* discloses PP1, but none of the applied references, either alone or in combination, teach or suggest inhibition of vascular permeability by PP1 to ameliorate tissue damage, as required by the claim.

Claim 16 is directly dependent on claim 1 and further defines the Src family tyrosine kinase inhibitor as being an inhibitor of Src tyrosine kinase (i.e., an inhibitor of Src, one of the many known Src family members, see e.g., Thomas *et al.*, pg. 516, appended to the Declaration of Cheresh of record). As noted above, Munshi *et al.* discloses PP1, which inhibits Src, but not VEGF; however, the applied references, alone or in combination, fail to teach or suggest that inhibition of Src will inhibit vascular permeability and ameliorate tissue damage as claimed.

Independent claim 17 is directed to an article of manufacture comprising a packaged pharmaceutical composition. The pharmaceutical composition is capable of modulating vascular permeability increase in a tissue suffering from a disease condition and

comprises a Src family tyrosine kinase inhibitor in a pharmaceutically acceptable carrier. The package includes a label indicating that the pharmaceutical composition can be used for treatment of vascular leakage or edema associated disease conditions.

As discussed above, no combination of the applied references teaches or suggests the essential connection between inhibition of a Src family tyrosine kinase and reduction in vascular permeability-associated edema and attendant tissue damage. Although Src family tyrosine kinase inhibitors are known in the art, the applied references do not teach or suggest the claimed limitation indicating that the Src family tyrosine kinase inhibitor is to be used to treat vascular leakage or edema associated disease conditions. Since the combined references do not teach or suggest all of the claim limitations, the obviousness rejection is improper and should be reversed.

Claim 18 is directly dependent on claim 17 and is specific for an article of manufacture in which the Src family tyrosine kinase inhibitor is a chemical inhibitor. Although Munshi *et al.* discloses a chemical inhibitor of Src family tyrosine kinases (PP1), the combined, applied references fail to teach or suggest that Src family tyrosine kinase inhibitors are to be used to inhibit vascular permeability.

Claim 19 is directly dependent on claim 18 and further defines the Src family tyrosine kinase inhibitor as being selected from seven specific chemical inhibitors including PP1. As noted above, Munshi *et al.* discloses PP1, albeit in connection with KS cell proliferation, but the applied references, alone or in combination, do not teach or suggest the necessary connection between Src kinase inhibition and treatment of vascular leakage and edema associated diseases using these specific chemical inhibitors.

Claim 20 is directly dependent on claim 18 and further defines the Src inhibitor as PP1. None of the applied references, either alone or in combination, teach or suggest inhibition of vascular permeability by PP1 to treat vascular leakage and edema associated disease, as required by the claim.

Claims 1-4 and 16-20 would not have been obvious to one or ordinary skill based on the teachings of any one of van Bruggen *et al.*, Aiello *et al.* or Jirousek in view of Munshi *et al.* This rejection should be reversed.

**B. Claims 1-4, inclusive, and 16-20, inclusive, would not have been obvious under 35 U.S.C. 103(a) from any one of van Bruggen *et al.*, Aiello *et al.* or Jirousek *et al.* in view of Hanke *et al.* and either of He *et al.* or Cooke *et al.***

Claims 1-4, inclusive, and 16-20, inclusive, stand rejected as being obvious under 35 U.S.C. 103(a) over any one of van Bruggen *et al.*, Aiello *et al.* or Jirousek *et al.* in view of Hanke *et al.* and either of He *et al.* or Cooke *et al.* This rejection is also unwarranted.

Shortcomings of teachings of van Bruggen *et al.*, Aiello *et al.* and Jirousek *et al.* as references against the appealed claims have been discussed in detail above. There also exists no valid basis for the attempted combination of the secondary references therewith.

Hanke *et al.* teaches that pyrazolopyrimidines PP1 and PP2 are potent inhibitors of selected members of the Src family of tyrosine kinases. In particular, Hanke *et al.* teaches that PP1 and PP2 are potent selective inhibitors of Lck and Fyn and also inhibit Src to a lesser extent. Hanke *et al.* does not teach or suggest, however, that vascular permeability and edema can be ameliorated by administration of a Src family tyrosine kinase inhibitor, as presently claimed.

He *et al.* teaches that VEGF induces nitric oxide production, which can be blocked by inhibition of Src kinase. This study does not address vascular permeability. He *et al.* utilized a battery of drugs, such as PP2, to identify which ones block VEGF-induced nitric oxide production in cultured cells, not vascular permeability. Contrary to the Examiner's contention on page 6 of the final Office Action (Paper No. 13), there is no suggestion in the reference to utilize a Src kinase inhibitor to treat vascular permeability. *A fortiori*, the reference teachings also do not provide a reasonable expectation of success for any such treatment. The Examiner notes that "effects of VEGF in stimulating angiogenesis and vascular permeability also require NOS activity." However, this does not mean, nor does the reference suggest, that inhibiting a Src family tyrosine kinase will reduce vascular permeability. In fact, He *et al.* supports Applicants' position of unobviousness.

He *et al.* unequivocally states at page 25130 that post-receptor signaling pathways of VEGF are not yet fully understood. See also Declaration of Cheresh, ¶ 12. Thus, the teachings of He *et al.* could not have provided any guidance, suggestion, or motivation to one of ordinary skill, to seek to ameliorate tissue damage due to edema or

vascular permeability by inhibiting a Src family tyrosine kinase. No reasonable expectation of success could have been derived by one of ordinary skill based on the foregoing teachings. He *et al.* does not provide any connection between PP2 inhibition and vascular permeability.

Cooke *et al.* teaches that PP2 inhibits VEGF stimulated VE-cadherin tyrosine phosphorylation, but provides no insight into vascular permeability. There is no suggestion in the reference itself that VE-cadherin bears any relationship to vascular permeability or edema. Cooke *et al.* does not cure any of the foregoing defects of Hanke *et al.* and He *et al.* as references against the present claims. Amelioration of tissue damage due to vascular permeability or edema by inhibition of Src family tyrosine kinase is neither mentioned nor suggested. Cooke *et al.* also provides no basis for the conjecture in the Final Office Action (Paper No. 13, page 6) that phosphorylation of VE-cadherin is the effector for the ..."increased vascular permeability signaled by VEGF," especially in view of the fact that even the role of VEGF in inducing vascular permeability is not fully understood. This is the Examiner's own, unsupported testimony. As such it cannot provide a valid basis for rejection. See also Declaration of Cheresh, ¶¶ 7, 12 and 20 in this regard.

Even assuming, *arguendo*, that the foregoing references are combinable, the combined references fail to teach or suggest the essential connection between inhibition of a Src family tyrosine kinase on one hand and reduction in vascular permeability and associated edema on the other. Absent such a teaching, the combined teachings of the applied references could not have possibly rendered claim 1 obvious to one of ordinary skill.

With regard to claim 2, neither van Bruggen *et al.*, Aiello *et al.*, nor Jirousek *et al.* even mention Src tyrosine kinases, much less any inhibitors thereof. Although Hanke *et al.*, He *et al.* and Cooke *et al.* do disclose chemical inhibitors of Src family tyrosine kinases (PP1, PP2), the requisite nexus between the primary references and the secondary references is missing. None of the applied references, alone or in combination, teach or suggest the required connection between chemical inhibitors of Src family tyrosine kinases and amelioration of tissue damage by inhibiting vascular permeability, as recited in claim 2.

With regard to claim 3, Hanke *et al.*, He *et al.* and Cooke *et al.* disclose chemical inhibitors of Src. The applied references, however, alone or in combination, fail to teach or suggest the essential connection between Src inhibition and inhibition of vascular

permeability by the specific chemical inhibitors of Src family tyrosine kinases, and thus could not have suggested the claimed method.

With regard to claim 4, Hanke *et al.*, He *et al.* and Cooke *et al.* disclose PP1 as a Src inhibitor, but none of the applied references, either alone or in combination, teach or suggest inhibition of vascular permeability by PP1 to ameliorate tissue damage, and thus could not have suggested the claimed method.

With regard to claim 16, Hanke *et al.*, He *et al.* and Cooke *et al.* disclose chemical inhibitors of Src (PP1, PP2), but none of the applied references, alone or in combination, teach or suggest that inhibition of Src will inhibit vascular permeability and ameliorate tissue damage. Thus, the claimed method could not have been suggested by the combined references.

With regard to claim 17, no combination of the applied references teaches or suggests the essential connection between inhibition of a Src family tyrosine kinase and reduction in vascular permeability-associated edema as discussed above. Although Src family tyrosine kinase inhibitors are known in the art (e.g., from Hanke *et al.*, He *et al.* and Cooke et al.), the applied references do not teach or suggest the claimed limitation of a label indicating that the Src family tyrosine kinase inhibitor can be used to treat vascular leakage or edema associated disease conditions. Since the combined references do not teach or suggest the claimed, packaged pharmaceutical composition, the obviousness rejection clearly is improper.

With regard to claim 18, while Hanke *et al.*, He *et al.* and Cooke *et al.* disclose chemical inhibitors of Src family tyrosine kinases, no combination of the applied references teaches or suggests the claimed connection between Src family tyrosine kinase inhibition and inhibition of vascular permeability. Nor does any combination of the references teach or suggest the claimed, packaged pharmaceutical composition that contains a chemical inhibitor of Src family tyrosine kinases can be utilized to treat vascular leakage and edema associated disease conditions. Thus, even the combined references could not have suggested the claimed, packaged pharmaceutical composition.

With regard to claim 19, Hanke *et al.*, He *et al.* and Cooke *et al.* disclose chemical inhibitors of Src; however, no combination of the applied references teaches or suggests that Src kinase inhibitors will inhibit vascular permeability to treat vascular

leakage and edema associated disease conditions. Accordingly, there is no suggestion of the claimed, packaged pharmaceutical composition.

With regard to claim 20, Hanke *et al.*, He *et al.* and Cooke *et al.* disclose PP1, but none of the applied references, either alone or in combination, teach or suggest inhibition of vascular permeability by PP1 to treat vascular leakage and edema associated disease conditions. Accordingly, the applied references could not have possibly suggested the claimed, packaged pharmaceutical composition.

Claims 1-4 and 16-20 would not have been obvious to one of ordinary skill from any one of van Bruggen *et al.*, Aiello *et al.* or Jirousek in view of Hanke *et al.* and either of He *et al.* or Cooke *et al.* This particular rejection should also be reversed.

C. **Claims 1-4, inclusive, and 16-20, inclusive, would not have been obvious under 35 U.S.C. 103(a) from any one of van Bruggen *et al.*, Aiello *et al.* or Jirousek *et al.* in view of Hanke *et al.* and Eliceiri *et al.* (1998)**

Claims 1-4, inclusive, and 16-20, inclusive, have been rejected as being obvious under 35 U.S.C. 103(a) over any one of van Bruggen *et al.*, Aiello *et al.* or Jirousek *et al.* in view of Hanke *et al.* and Eliceiri *et al.* (1998). This rejection is unwarranted as well.

Van Bruggen *et al.*, Aiello *et al.*, Jirousek *et al.* and Hanke *et al.* have been discussed in detail above. The same shortcomings of these references are applicable here, and are not cured by the citation of yet another reference, co-authored by one of the present Appellants. Eliceiri *et al.* (1998) teaches that mutationally inactive Src (i.e., Src lacking a kinase domain) disrupted VEGF-induced angiogenesis in a chick chorioallantoic membrane model, while mutationally active Src-induced angiogenesis. Eliceiri *et al.* (1998) also teaches that both mutationally active Src-induced angiogenesis and VEGF-induced angiogenesis can be inhibited by antagonists to integrin $a_v\beta_5$ but not integrin $a_v\beta_3$. The reference mentions neither vascular permeability nor edema. Nor does the reference teach that angiogenesis and vascular permeability are necessarily coupled. At best, combination of Eliceiri *et al.* (1998) with Van Bruggen *et al.*, Aiello *et al.*, Jirousek *et al.* and Hanke *et al.* is an invitation to experiment, albeit without a reasonable expectation of success. In light of the complex nature of VEGF signaling, the contradictory teachings of the art with regard to effects of VEGF on edema and the extreme complexity of the interaction of Src family tyrosine kinases with other signaling pathways, one of ordinary skill would not have

combined the teachings of these references in the first place. In addition, the combined references would not have suggested the method of claim 1 in any event.

With regard to claim 2, van Bruggen *et al.*, Aiello *et al.*, and Jirousek *et al.* do not mention Src tyrosine kinases at all, much less inhibitors thereof. Hanke *et al.* discloses chemical inhibitors of Src family tyrosine kinases, and Eliceiri *et al.* (1998) relates Src kinase activity to angiogenesis. None of the applied references, however, alone or in combination, teach or suggest the required connection between chemical inhibitors of Src family tyrosine kinases and amelioration of tissue damage by inhibiting vascular permeability. Thus the method as recited in claim 2 could not have possibly been suggested by the combined teachings of these references.

With regard to claim 3, Hanke *et al.* discloses chemical inhibitors of Src and Eliceiri *et al.* relates Src activity to angiogenesis as noted above. The applied references, however, alone or in combination, fail to teach or suggest the claimed connection between Src inhibition and inhibition of vascular permeability by the specific chemical inhibitors recited in claim 3. Accordingly, the claimed method could not have been suggested to one of ordinary skill by these references.

With regard to claim 4, this claim further defines the Src family tyrosine kinase inhibitor as PP1. While Eliceiri *et al.*, discloses that Src activity is associated with angiogenesis, none of the applied references, either alone or in combination, teach or suggest inhibition of vascular permeability by PP1 to ameliorate tissue damage, as required by the claimed method. Thus, the combined references would not have suggested the claimed method to one of ordinary skill.

With regard to claim 16, while Eliceiri *et al.* discloses that Src activity is associated with angiogenesis, none of the applied references, alone and in combination, teach or suggest that inhibition of Src will inhibit vascular permeability and ameliorate tissue damage. Again, the claimed method could not have been suggested to one of ordinary skill by the combined teachings of the applied references.

With regard to claim 17, none of the applied references, nor any combination thereof, teaches or suggests that the inhibition of a Src family tyrosine kinase will result in reduction in vascular permeability-associated edema. Although Src family tyrosine kinase inhibitors are known in the art (e.g., from Hanke *et al.*) and Src kinase activity is associated with angiogenesis (Eliceiri *et al.*), the applied references do not teach or suggest

the claimed, packaged pharmaceutical composition with a label indicating that Src family tyrosine kinase inhibitors can be used to treat vascular leakage or edema associated disease conditions. The combined references do not teach or suggest all of the claim limitations and thus cannot sustain an obviousness rejection.

With regard to claim 18, no combination of the applied references teaches or suggests the claim limitation that chemical inhibitors of Src family tyrosine kinases can modulate vascular permeability. Nor does any combination of the references teach or suggest that the claimed pharmaceutical composition containing a chemical inhibitor of Src family tyrosine kinases and bearing a label indicating that this composition can be utilized to treat vascular leakage and edema associated disease conditions. Accordingly, the claimed, packaged pharmaceutical composition could not have been suggested to one of ordinary skill by the applied references.

With regard to claim 19, the limitations of the applied references are equally apparent. No combination of the references teaches or suggests all of the limitations of this claim. Hanke *et al.* and Eliceiri *et al.* (1998) fail to overcome the deficiencies of van Bruggen *et al.*, Aiello *et al.*, and Jirousek *et al.* in this regard. Therefore, even the combined references would not have suggested the claimed pharmaceutical composition to one of ordinary skill.

With regard to claim 20, this claim also would not have been obvious from the applied references. Van Bruggen *et al.*, Aiello *et al.*, and Jirousek *et al.* are silent with regard to Src kinase. Hanke *et al.* only discloses PP1 as an inhibitor of Src kinase, and Eliceiri *et al.* relates Src kinase activity only to angiogenesis. None of the applied references, either alone or in combination, teach or suggest inhibition of vascular permeability by PP1 to treat vascular leakage and edema associated disease conditions. The claimed packaged composition would not have been suggested to one of ordinary skill by such references.

Given the complexity of Src kinase and VEGF signaling pathways and the conflicting results reported by van Bruggen *et al.*, Hayashi *et al.* and Bao *et al.* with respect to the effect of interfering with VEGF signaling on edematous tissue, one of skill in the art would not have been motivated use Src family tyrosine kinase inhibitors to inhibit vascular leakage and edema with any reasonable expectation of success. Without

impermissible reference to the present application, the Examiner could not have possibly arrived at the attempted reference combinations.

**9. Conclusion**

Claims 1-4, inclusive and 16-20, inclusive, would not have been obvious from van Bruggen *et al.*, Aiello *et al.* or Jirousek *et al.* in view of any one of, or any combination of, Munshi *et al.*, Hanke *et al.*, He *et al.*, Cooke *et al.* or Eliceiri *et al.* (1998). The applied references do not teach or suggest all of the limitations of the claimed methods and articles of manufacture for ameliorating tissue damage related to vascular leakage or edema.

No valid basis for the various attempted combinations of references has been established. The Examiner's own testimony as to the proprietary of the attempted combinations, unsupported by the record, is of no moment. Moreover, the applied references, even if combined, could not have suggested the claimed invention to one of ordinary skill in the art. Reversal of the rejections of all claims is earnestly urged.

Respectfully submitted,

Dated 2 June 2003

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# APPENDIX I

## CLAIMS ON APPEAL

Claim 1 (original). A method for ameliorating tissue damage related to vascular leakage or edema comprising contacting said tissue with a vascular permeability modulating amount of a pharmaceutical composition comprising a Src family tyrosine kinase inhibitor.

Claim 2 (original). The method of claim 1 wherein said Src family tyrosine kinase inhibitor is a chemical inhibitor.

Claim 3 (previously amended). The method of claim 2 wherein said chemical inhibitor is selected from the group consisting of pyrazolopyrimidine PP1, pyrazolopyrimidine PP2, PD173955, AGL1872, PD162531, Radicol R2146 and Geldanamycin.

Claim 4 (previously amended). The method of claim 3 wherein said inhibitor is pyrazolopyrimidine PP1.

Claim 16 (original). A method of claim 1 wherein said inhibitor is a Src tyrosine kinase inhibitor.

Claim 17 (original). An article of manufacture comprising packaging material and a pharmaceutical composition contained within said packaging material, wherein said pharmaceutical composition is capable of modulating vascular permeability increase in a tissue suffering from a disease condition, wherein said packaging material comprises a label which indicates that said pharmaceutical composition can be used for treatment of vascular leakage or edema associated disease conditions, and wherein said pharmaceutical composition comprises a Src family tyrosine kinase inhibitor and a pharmaceutically acceptable carrier therefor.

Claim 18 (original). An article of manufacture of claim 17 wherein said Src family tyrosine kinase inhibitor is a chemical inhibitor.

Claim 19 (previously amended). An article of manufacture of claim 18 wherein said Src family tyrosine kinase inhibitor is selected from the group consisting of pyrazolopyrimidine PP1, pyrazolopyrimidine PP2, PD173955, AGL1872, PD162531, Radicol R2146 and Geldanamycin.

Claim 20 (previously amended). An article of manufacture of claim 18 wherein said Src family tyrosine kinase inhibitor is pyrazolopyrimidine PP1.

APPENDIX II

DORLAND'S ILLUSTRATED

# Medical Dictionary

*Twenty-fifth Edition*

W. B. SAUNDERS · Philadelphia · London · Toronto

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**ectrogenic** (ek"tro-jen'ik) pertaining to or characterized by ectrogeny.

**ectrogeny** (ek-troj'ĕ-ne) [Gr. *ektrōma* abortion + *gennan* to produce] congenital absence or defect of a part.

**ectromelia** (ek"tro-me'le-ah) gross hypoplasia or aplasia of one or more long bones of one or more limbs; the term includes amelia, hemimelia, and phocomelia. **infectious e.,** a disease of mice caused by a poxvirus and characterized by gangrene and often loss of one or more of the feet and sometimes of other external parts, and by necrotic areas in the liver, spleen, and other organs; called also *mousepox*.

**ectromelic** (ek"tro-mel'ik) pertaining to or characterized by ectromelia.

**ectromelus** (ek-trom'ĕ-lus) [Gr. *ektrōma* abortion + *melos* limb] an individual exhibiting ectromelia.

**ectrometacarpia** (ek"tro-met"ah-kar'pe-ah) [Gr. *ektrōma* abortion + *metacarpus* + *-ia*] congenital absence of a metacarpal bone.

**ectrometatarsia** (ek"tro-met"ah-tar'se-ah) [Gr. *ektrōma* abortion + *metatarsus* + *-ia*] congenital absence of a metatarsal bone.

**ectrophalangia** (ek"tro-fah-lan'je-ah) congenital absence of one or more phalanges of a digit.

**ectropion** (ek-tro'pe-on) [Gr. "an everted eyelid"; *ektropē* a turning aside] the turning outward (eversion) of an edge or margin, as of the eyelid, resulting in exposure of the palpebral conjunctiva. **cervical e.,** eversion of uterine cervix. **e. cicatri'ceum, cicatricial e.,** eversion of the margin of an eyelid caused by contraction of scar tissue in the lid or by contraction of the skin. **flaccid e.,** ectropion of the lower lid resulting from reduced tone of the orbicularis oculi muscle. **e. luxu'rians,** e. sarcomatosum. **paralytic e., e. paralyt'icum,** eversion of the margin of the lower eyelid as a result of paralysis of the facial nerve, and loss of contractile power of the orbicularis oculi muscle. **e. of pigment layer,** proliferation of the cells in the posteriorly situated pigment layer of the iris, leading to their migration around the pupillary margin to encroach upon the anterior surface of the iris. **e. sarcomato'sum,** eversion of an eyelid resulting from chronic thickening of the palpebral conjunctiva; called also *e. luxurians*. **senile e., e. seni'lis,** eversion of the lower eyelid associated with relaxation of the fibers of the palpebral portion of the orbicularis oculi muscle as a concomitant of age, or occurring as a result of atrophic changes in the skin. **spastic e., e. spas'ticum,** ectropion caused by tonic spasm of the orbicularis oculi muscle. **e. u'veae,** eversion of the margin of the pupil, often congenital (*e. u'veae congen'itum*), and frequently due to the presence of a newly formed membrane on the anterior layer of the iris, or to the formation of connective tissue in the stroma, particularly in diabetes. Called also *tridectropium*.

**ectropionize** (ek-tro'pe-ō-niz") to put into a state of eversion.

**ectropium** (ek-tro'pe-um) ectropion.

**ectrosis** (ek-tro'sis) [Gr. *ektrosis*] 1. abortion. 2. treatment that arrests the development of disease.

**ectrosyndactylia** (ek"tro-sin"dak-til'e-ah) ectrosyndactyly.

**ectrosyndactyly** (ek"tro-sin-dak'ti-le) [Gr. *ektroma* abortion + *syn* together + *daktylos* finger] a condition in which some of the digits are missing and those that remain are webbed, so that they are more or less attached.

**ectrotic** (ek-trot'ik) 1. pertaining to or producing abortion. 2. arresting the development of a disease.

**ectylurea** (ek"til-u-re'ah) chemical name: cis-(2-ethylcrotonyl)urea. A white crystalline powder, $C_7H_{12}N_2O_2$, used as a sedative.

**ectyonin** (ek"ti-on'in) an antimicrobial substance obtained from the sponge *Microciona prolifera*.

**ectype** (ek'tip) an unusual type of physical or mental constitution.

**ectypia** (ek-ti'pe-ah) deviation from type; the possession of an unusual type of constitution.

**eczema** (ek'zĕ-mah) [Gr. *ekzein* to boil out] 1. a superficial inflammatory process involving primarily the epidermis, characterized early by redness, itching, minute papules and vesicles, weeping, oozing, and crusting, and later by scaling, lichenification, and often pigmentation. It is not a disease entity or an acceptable diagnosis. 2. atopic dermatitis. **allergic e.** (*obs.*), allergic dermatitis. **atopic e.** (*obs.*), see under *dermatitis*. **e. capi'tis** (*obs.*), seborrheic dermatitis or allergic contact dermatitis of the scalp. **contact e.,** contact dermatitis (def. 1). **e. ep'ilans** (*obs.*), eczema with loss of hair. **e. epizoot'ica,** foot-and-mouth disease. **facial e. of ruminants,** a photosensitive disease of ruminants, particularly in New Zealand, due to ingestion of the spores of the mold *Pithomyces chartarum* (class Deuteromycetes), which contain sporidesmin. **flexural e.,** atopic dermatitis. **e. herpet'icum,** disseminated herpes simplex; see also *Kaposi's varicelliform eruption*. **impetiginous e.,** infectious eczematoid dermatitis. **infantile e.,** atopic dermatitis in infants. Called also *Besnier's prurigo* (in Britain). **e. intertri'go,** intertrigo. **e. margina'tum,** tinea cruris. **nummular e., e. nummula're,** eczema in which the patches are coin shaped; it may be a form of neurodermatitis. **orbicular e.,** nummular e. **seborrheic e., e. seborrhoe'icum** (*obs.*), seborrheic dermatitis. **solar e., e. sola're** (*obs.*), polymorphous light eruption. **stasis e.,** stasis dermatitis. **e. vaccina'tum,** disseminated vaccinia; see also *Kaposi's varicelliform eruption*.

**eczematid, eczematide** (ek-zem'ah-tid) loosely, an eczematous lesion not caused by external contact-type allergy, or by infection in the involved area; the term has different uses in different countries and little currency in the United States.

**eczematization** (ek-zem"ah-ti-za'shun) persistent eczema-like lesions of the skin, usually due to the continued trauma of scratching.

**eczematogenic** (ek-zem"ah-to-jen'ik) causing eczema.

**eczematoid** (ek-zem'ah-toid) resembling eczema.

**eczematous** (ek-zem'ah-tus) affected with or of the nature of eczema.

**E.D.** erythema dose; effective dose.

**$E.D._{50}$** median effective dose; a dose that produces its effects in 50 per cent of a population.

**edathamil** (ĕ-dath'ah-mil) edetate.

**Eddowes' syndrome (disease)** (ed'ōz) [Alfred *Eddowes*, British physician, 1850–1946] see under *syndrome*.

**Edebohls' operation, position** (ed'e-bōlz) [George Michael *Edebohls*, New York surgeon, 1853–1908] see under *operation* and *position*.

**Edelman,** Gerald Maurice. American biochemist, born 1929, co-winner, with Rodney Porter, of the Nobel prize in physiology and medicine for 1972, for his work on the chemical structure of antibodies.

**Edelmann's anemia, cell** (a'del-manz) [Adolf *Edelmann*, physician in Vienna, 1885–1939] see under *anemia*, and see *kinetocyte*.

**edema** (ĕ-de'mah) [Gr. *oidēma* swelling] the presence of abnormally large amounts of fluid in the intercellular tissue spaces of the body; usually applied to demonstrable accumulation of excessive fluid in the subcutaneous tissues. **acute circumscribed e., acute essential e.,** angioneurotic e. **alimentary e.,** nutritional edema. **ambulant e.** (*obs.*), Calabar swelling; see under *swelling*. **angioneurotic e.,** a condition characterized by the sudden appearance of temporary edematous areas of the skin or mucous membranes and occasionally of the viscera, often associated with dermographia, urticaria, erythema, and purpura, which may be of allergic, neurotic, or of unknown origin. Called also *acute circumscribed e., Milton's e., Quincke's e., wandering e., giant urticaria*, etc. **angioneurotic e., hereditary,** a form similar to the nonhereditary form but tending to involve more visceral lesions, especially of the respiratory and gastrointestinal tracts. Two types, both autosomal dominant traits, are distinguished: one involves failure of synthesis of the inhibitor of complement component C1, the other involves the synthesis of an abnormal protein. **e. artefac'tum,** edema that is artificially produced. **Berlin's e.,** commotio retinae.

**blue e.,** a puffed, bluish appearance of a limb in hysterical paralysis. **brain e.,** an excessive accumulation of fluid in the brain substance (*wet brain*); it may be due to various causes, including trauma, tumor, and increased permeability of the capillaries occurring as a result of anoxia or exposure to toxic substances. **brown e.,** hardening and infiltration of the lung with a brownish fluid. **e. bullo'sum vesi'cae,** a condition of the mucous lining of the bladder marked by the formation of clear vesicles with small white particles floating between them. **Calabar e.,** Calabar swellings. **e. cal'idum,** inflammatory e. **cardiac e.,** a manifestation of congestive heart failure, caused by increased venous and capillary pressures and often associated with the retention of sodium by the kidneys. **circumscribed e.,** angioneurotic e. **dependent e.,** edema affecting most seriously the lowermost or dependent parts of the body. **famine e.,** nutritional e. **fingerprint e.,** edema in which the whorls of the fingerprint are clearly visible after circumferential manipulation of a pressure point on the forehead or sternum, considered indicative of intracellular fluid excess. **e. frig'idum,** noninflammatory e. **e. fu'gax,** transient accumulation of fluid in a specific region. **gaseous e.,** edema accompanied with gas formation, as in gas bacillus infection and subcutaneous emphysema. **giant e.,** angioneurotic e. **hepatic e.,** edema due to faulty functioning of the liver. **high-altitude pulmonary e.,** pulmonary edema caused by hypoxia that develops as a result of prolonged exertion after ascending quickly to high altitudes without the benefit of acclimatization; seen especially in mountain climbers. **Huguenin's e.,** acute congestive edema of the brain. **hunger e.,** nutritional e. **hydremic e.,** edema in conditions marked by hydremia. **hysterical e.,** blue e. **idiopathic e.,** edema of unknown cause affecting women, occurring intermittently over a period of years and usually worse during the premenstrual phase; it is associated with increased aldosterone secretion. **inflammatory e.,** a form due to inflammation, and attended with redness and pain. **insulin e.,** edema which sometimes follows the injection of insulin. **invisible e.,** the accumulation of a considerable amount of fluid in the subcutaneous tissues before it becomes demonstrable. **local intracutaneous e.,** urticaria. **e. of lung,** pulmonary e. **lymphatic e.,** edema associated with obstruction of the lymph vessels. **malignant e.,** edema marked by rapid extension, with destruction of tissue and formation of a gas. **migratory e.,** angioneurotic e. **Milroy's e.,** see under *disease*. **Milton's e.,** angioneurotic e. **mucous e.,** myxedema. **e. neonato'rum,** a disease of premature and feeble infants that resembles sclerema and is marked by spreading edema with cold, livid skin. **nephrotic e.,** edema occurring in nephrosis and in the intermediate stage of diffuse nephritis. **neuropathic e.,** pseudolipoma. **noninflammatory e.,** edema without redness and pain, occurring from passive congestion or from lowered serum osmolarity. **nonpitting e.,** edema in which the tissues cannot be pitted by pressure. **nutritional e.,** a disorder of nutrition due to long-continued diet deficiency of protein and/or calories, and marked by anasarca and edema; called also *alimentary e., famine e., war e., hunger e.,* and *nutritional, famine,* or *war dropsy*. **paroxysmal pulmonary e.,** pulmonary edema marked by nocturnal attacks of difficult respiration, audible rales, wheezes, and cough, caused by acute left ventricular failure, usually associated with hypertensive heart disease. **passive e.,** edema occurring because of obstuction to vascular or lymphatic drainage from the area. **periodic e.,** angioneurotic e. **periretinal e.,** central serous retinopathy. **Pirogoff's e.,** malignant e. **pitting e.,** edema in which the tissues show prolonged existence of the pits produced by pressure. **placental e.,** the presence of fluid in the villi of the placenta, the villi being club-shaped and irregularly swollen. **prehepatic e.,** edema occurring in prehepatic hypoproteinemia. **pulmonary e.,** abnormal, diffuse, extravascular accumulation of fluid in the pulmonary tissues and air spaces due to changes in hydrostatic forces in the capillaries or to increased capillary permeability; it is characterized clinically by intense dyspnea and, in the intra-alveolar form, by voluminous expectoration of frothy pink serous fluid and, if severe, by cyanosis. **purulent e.,** a swelling due to the effusion of a purulent fluid. **Quincke's e.,** angioneurotic e. **renal e.,** edema due to nephritis and the consequent hypoproteinemia. **rheumatismal e.,** painful red edematous swellings on the limbs in rheumatism, due to subcutaneous exudation. **salt e.,** edema produced by an increase of sodium chloride in the diet. **solid e.,** myxedema. **solid e. of lungs,** a rubbery consistency and gelatinous appearance of the lungs sometimes associated with hypertensive left ventricular failure and uremia. **terminal e.,** pulmonary edema which frequently develops as an agonal event from circulatory failure. **toxic e.,** edema caused by a poison. **venous e.,** edema in which the effused liquid comes from the blood. **vernal e. of lung,** edema of the lung occurring in spring and considered to be allergic. **wandering e.,** angioneurotic e. **war e.,** nutritional e.

**edematigenous** (ĕ-dem"ah-tij'ĕ-nus) edematogenic.

**edematization** (ĕ-dem"ah-ti-za'shun) the process of becoming or of making edematous.

**edematogenic** (ĕ-dem"ah-to-jen'ik) producing or causing edema.

**edematous** (ĕ-dem'ah-tus) pertaining to or affected by edema.

**Edentata** (e"den-ta'tah) an order of mammals including armadillos, tree sloths, and anteaters.

**edentate** (e-den'tāt) edentulous.

**edentia** (e-den'she-ah) [L. *e* without + *dens* tooth] absence of the teeth.

**edentulate** (e-den'tu-lāt) edentulous.

**edentulous** (e-den'tu-lus) [L. *e* without + *dens* tooth] without teeth; having lost the natural teeth.

**edetate** (ed'ĕ-tāt) ethylenediaminotetraacetate. Any salt of edetic acid; called also *edathamil*. Abbreviated EDTA. **e. calcium disodium, calcium disodium e.** [USP], chemical name: disodium [(ethylenedinitrilo)-tetraacetato]calciate(2−). A metal complexing agent, $C_{10}H_{12}CaN_2Na_2O_8 \cdot xH_2O$, consisting of a mixture of the dihydrate and trihydrate of calcium disodium ethylenediaminetetraacetate (predominantly the dihydrate), used in the diagnosis and treatment of lead poisoning. Called also *calcium edathamil* and *calciumedetate sodium*. **e. disodium or disodium e.** [USP], a white crystalline powder, $C_{10}H_{14}N_2Na_2O_8 \cdot H_2O$, freely soluble in water, used as a chelating agent in poisoning with lead and other heavy metals and, because of its affinity for calcium, in the treatment of hypercalcemia. Called also *edathamil disodium*. **e. sodium,** the sodium salt of ethylenediaminotetraacetate, a chelating agent. **e. trisodium,** the trisodium salt of ethylenediaminotetraacetate; a chelating agent.

**edge** (ej) a thin side or border. **cutting e.,** the angle formed by the merging of two flat surfaces, by which something may be cut, such as the blade of a knife, or the incisal surface of an anterior tooth. **denture e.,** see under *border*. **incisal e.,** the junction of the labial surface of an anterior tooth with a flattened linguoincisal surface created by occlusal wear.

**edge-strength** (ej' strength) the resistance offered by an edge to a fracturing force, applied especially in dentistry to such resistance offered by the edge of an amalgam restoration.

**Edinger's law, nucleus** (ed'ing-gerz) [Ludwig *Edinger*, German neurologist, 1855–1918] see under *law* and *nucleus*.

**Edinger-Westphal nucleus** (ed'ing-ger-vest'fahl) [L. *Edinger*; Carl Friedrich Otto *Westphal*, German neurologist, 1833–1890] nucleus accessorius.

**edipism** (ed'ĭ-pizm) [from *Oedipus*, King of Thebes. See *Oedipus complex*] intentional injury of one's own eyes.

**Edlefsen's reagent test** (ed'lef-senz) [Gustav J. J. F *Edlefsen*, German physician, 1842–1910] see under *reagent*.

**EDR** effective direct radiation; electrodermal response.

**edrophonium chloride** (ed"ro-fo'ne-um) [USP] chemical name: (*m*-hydroxyphenyl) dimethylam-

apparently chemically identical with bilirubin but which has a different site of origin, being formed locally in the tissues from hemoglobin, particularly under conditions of reduced oxygen tension.

**hematokolpos** (hem″ah-to-kol′pos) hematocolpos.

**hematokrit** (he-mat′o-krit) hematocrit.

**hematolin** (hem″ah-to′lin) a compound, $C_{68}H_{72}O_7N_8$, from heme.

**hematolith** (hem′ah-to-lith) (*obs.*) hemolith.

**hematologist** (hem″ah-tol′o-jist) a specialist in the study of the blood.

**hematology** (hem″ah-tol′o-je) [*hemato-* + *-logy*] that branch of medical science which treats of the morphology of the blood and blood-forming tissues.

**hematolymphangioma** (hem″ah-to-lim″fan-je-o′mah) [*hemato-* + L. *lympha* lymph + Gr. *angeion* vessel + *-oma*] a tumor composed of blood vessels and lymph vessels.

**hematolysis** (hem″ah-tol′ĭ-sis) hemolysis.

**hematolytic** (hem″ah-to-lit′ik) hemolytic.

**hematoma** (hem″ah-to′mah), pl. *hemato′mas* [*hemato-* + *-oma*] a localized collection of blood, usually clotted, in an organ, space, or tissue, due to a break in the wall of a blood vessel. **aneurysmal h.,** false aneurysm. **h. au′ris,** hematoma of the perichondrium of the ear. **epidural h.,** accumulation of blood in the epidural space, due to damage to the middle meningeal artery and producing compression of the dura mater and thus compression of the brain. Unless evacuated, it may result in herniation through the tentorium, and death. **pelvic h.,** a collection of blood in the pelvic cellular tissue. **perianal h.,** a hematoma under the perianal skin, caused by rupture of a subcutaneous vessel, the blood being kept localized by fibroelastic septa and causing much pain. **retrouterine h.,** an effusion of blood into the retrouterine connective tissue. **subdural h.,** accumulation of blood in the subdural space. In the severe *acute* form, both blood and cerebrospinal fluid enter the space as a result of laceration of the brain and a tear in the arachnoid, adding subdural compression to the direct injury to the brain. In the *chronic* form, only blood effuses into the subdural space as a result of rupture of the bridging veins, usually due to closed head injury. The effusion is a gradual process resulting, weeks after the injury, in headache, progressive stupor, and hemiparesis, followed by dilating pupil, a sign of herniation of the tentorium. **subungual h.,** an accumulation of blood under the nail plate.

**hematomancy** (hem′ah-to-man-se) [*hemato-* + Gr. *manteia* divination] diagnosis by examination of the blood.

**hematomanometer** (hem″ah-to-mah-nom′ĕter) sphygmomanometer.

**hematomediastinum** (hem″ah-to-me″de-as-ti′num) [*hemato-* + *mediastinum*] hemomediastinum.

**hematometakinesis** (hem″ah-to-met″ah-ki-ne′sis) [*hemato-* + Gr. *meta* across + *kinesis* movement] the phenomenon of the shifting of blood from one part of the body to another, as from the skin to the internal organs; called also *borrowing-lending hemodynamic phenomenon.*

**hematometer** (hem″ah-tom′ĕ-ter) [*hemato-* + Gr. *metron* measure] a hemoglobinometer.

**hematometra** (hem″ah-to-me′trah) [*hemato-* + Gr. *mētra* uterus] an accumulation of blood in the uterus.

**hematometry** (hem″ah-tom′ĕ-tre) [*hemato-* + Gr. *metron* measure] measurement of the hemoglobin and estimation of the percentage of the various cells in the blood.

**hematomole** (he-mat′o-mōl) Breus' mole.

**hematomphalocele** (hem″at-om-fal′o-sēl) [*hemat-* + *omphalocele*] an umbilical hernia containing blood.

**hematomphalus** (hem″at-om′fah-lus) Cullen's sign; see under *sign.*

**hematomycosis** (hem″ah-to-mi-ko′sis) (*obs.*) fungemia.

**hematomyelia** (hem″ah-to-mi-e′le-ah) [*hemato-* + Gr. *myelos* marrow + *-ia*] hemorrhage into the spinal cord, usually confined to the gray substance, most often due to trauma, and marked by the sudden onset of flaccid paralysis with sensory disturbances.

**hematomyelitis** (hem″ah-to-mi″ĕ-li′tis) [*hemato-* + *myelitis*] acute myelitis with bloody effusion within the spinal cord.

**hematomyelopore** (hem″ah-to-mi′el-o-pōr″) [*hemato-* + Gr. *myelos* marrow + *poros* opening] a disease marked by the formation of canals in the spinal cord, due to hemorrhage.

**hematoncometry** (hem″at-on-kom′ĕ-tre) [*hemat-* + Gr. *onkos* mass + *metron* measure] measurement of blood volume.

**hematonephrosis** (hem″ah-to-nĕ-fro′sis) presence of blood in the pelvis of the kidney.

**hematonic** (hem″ah-ton′ik) a blood tonic.

**hematonosis** (hem″ah-ton′o-sis) any disease of the blood.

**hematopathology** (hem″ah-to-pah-thol′o-je) hemopathology.

**hematopedesis** (hem″ah-to-pĕ-de′sis) hemodiapedesis.

**hematopenia** (hem″ah-to-pe′ne-ah) [*hemato-* + Gr. *penia* poverty] deficiency of blood.

**hematopericardium** (hem″ah-to-per″ĭ-kar′de-um) hemopericardium.

**hematoperitoneum** (hem″ah-to-per″ĭ-to-ne′um) hemoperitoneum.

**hematopexin** (hem″ah-to-pek′sin) hemopexin.

**hematopexis** (hem″ah-to-pek′sis) hemopexis.

**hematophage** (hem′ah-to-fāj) hemophagocyte.

**hematophagia** (hem″ah-to-fa′je-ah) 1. blood drinking. 2. the act of subsisting on the blood of another animal. 3. hemocytophagia.

**hematophagocyte** (hem″ah-to-fag′o-sīt) hemophagocyte.

**hematophagous** (hem″ah-tof′ah-gus) [*hemato-* + Gr. *phagein* to eat] pertaining to or characterized by hematophagia.

**hematophagy** (hem″ah-tof′ah-je) hematophagia.

**hematophilia** (hem″ah-to-fil′e-ah) hemophilia.

**hematophyte** (hem′ah-to-fit″) [*hemato-* + Gr. *phyton* plant] (*obs.*) any vegetable microorganism or species living in the blood.

**hematophytic** (hem″ah-to-fit′ik) (*obs.*) pertaining to or caused by hematophytes.

**hematopiesis** (hem″ah-to-pi′ĕ-sis) [*hemato-* + Gr. *piesis* pressure] blood pressure.

**hematoplasmopathy** (hem″ah-to-plaz-mop′ah-the) [*hemato-* + *plasma* + Gr. *pathos* disease] any disorder due to alteration of the protein constitution of the blood.

**hematoplast** (hem′ah-to-plast) hemocytoblast.

**hematoplastic** (hem″ah-to-plas′tik) [*hemato-* + Gr. *plassein* to mold] concerned in the elaboration of the blood.

**hematopoiesis** (hem″ah-to-poi-e′sis) [*hemato-* + Gr. *poiein* to make] the formation and development of blood cells. **extramedullary h.,** the formation and development of blood cells outside the bone marrow, as in the spleen, liver, and lymph nodes.

**hematopoietic** (hem″ah-to-poi-et′ik) [*hemato-* + Gr. *poiein* to make] 1. pertaining to or affecting the formation of blood cells. 2. an agent that promotes the formation of blood cells.

**hematopoietin** (hem″ah-to-poi′e-tin) erythropoietin.

**hematoporphyria** (hem″ah-to-por-fi′re-ah) porphyria.

**hematoporphyrin** (hem″ah-to-por′fĭ-rin) [*hemato-* + Gr. *porphyra* purple] chemical name: 1,3,5,8-tetramethyl-2,4-bis(α-hydroxyethyl)-6,7-dipropionic acid porphin. A dark violet, iron-free powder resulting from decomposition of hemoglobin, with the addition of HOH to the vinyl groups.

**hematoporphyrinemia** (hem″ah-to-por-fĭ-rin-e′me-ah) the presence of hematoporphyrin in the blood.

**hematoporphyrinism** (hem″ah-to-por′fĭ-rin-izm) a state characterized by hematoporphyrinemia and a sensitiveness to sunlight.

**APPENDIX II**

# *DORLAND'S ILLUSTRATED*

# *Medical Dictionary*

*Twenty-fifth Edition*

W. B. SAUNDERS · Philadelphia · London · Toronto

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**ectrogenic** (ek"tro-jen'ik) pertaining to or characterized by ectrogeny.

**ectrogeny** (ek-troj'ĕ-ne) [Gr. *ektrōma* abortion + *gennan* to produce] congenital absence or defect of a part.

**ectromelia** (ek"tro-me'le-ah) gross hypoplasia or aplasia of one or more long bones of one or more limbs; the term includes amelia, hemimelia, and phocomelia. **infectious e.,** a disease of mice caused by a poxvirus and characterized by gangrene and often loss of one or more of the feet and sometimes of other external parts, and by necrotic areas in the liver, spleen, and other organs; called also *mousepox*.

**ectromelic** (ek"tro-mel'ik) pertaining to or characterized by ectromelia.

**ectromelus** (ek-trom'ĕ-lus) [Gr. *ektrōma* abortion + *melos* limb] an individual exhibiting ectromelia.

**ectrometacarpia** (ek"tro-met"ah-kar'pe-ah) [Gr. *ektrōma* abortion + *metacarpus* + *-ia*] congenital absence of a metacarpal bone.

**ectrometatarsia** (ek"tro-met"ah-tar'se-ah) [Gr. *ektrōma* abortion + *metatarsus* + *-ia*] congenital absence of a metatarsal bone.

**ectrophalangia** (ek"tro-fah-lan'je-ah) congenital absence of one or more phalanges of a digit.

**ectropion** (ek-tro'pe-on) [Gr. "an everted eyelid"; *ektropē* a turning aside] the turning outward (eversion) of an edge or margin, as of the eyelid, resulting in exposure of the palpebral conjunctiva. **cervical e.,** eversion of uterine cervix. **e. cicatri'ceum, cicatricial e.,** eversion of the margin of an eyelid caused by contraction of scar tissue in the lid or by contraction of the skin. **flaccid e.,** ectropion of the lower lid resulting from reduced tone of the orbicularis oculi muscle. **e. luxu'rians,** e. sarcomatosum. **paralytic e., e. paralyt'icum,** eversion of the margin of the lower eyelid as a result of paralysis of the facial nerve, and loss of contractile power of the orbicularis oculi muscle. **e. of pigment layer,** proliferation of the cells in the posteriorly situated pigment layer of the iris, leading to their migration around the pupillary margin to encroach upon the anterior surface of the iris. **e. sarcomato'sum,** eversion of an eyelid resulting from chronic thickening of the palpebral conjunctiva; called also *e. luxurians*. **senile e., e. seni'lis,** eversion of the lower eyelid associated with relaxation of the fibers of the palpebral portion of the orbicularis oculi muscle as a concomitant of age, or occurring as a result of atrophic changes in the skin. **spastic e., e. spas'ticum,** ectropion caused by tonic spasm of the orbicularis oculi muscle. **e. u'veae,** eversion of the margin of the pupil, often congenital (*e. u'veae congen'itum*), and frequently due to the presence of a newly formed membrane on the anterior layer of the iris, or to the formation of connective tissue in the stroma, particularly in diabetes. Called also *iridectropium*.

**ectropionize** (ek-tro'pe-ō-nīz") to put into a state of eversion.

**ectropium** (ek-tro'pe-um) ectropion.

**ectrosis** (ek-tro'sis) [Gr. *ektrōsis*] 1. abortion. 2. treatment that arrests the development of disease.

**ectrosyndactylia** (ek"tro-sin"dak-til'e-ah) ectrosyndactyly.

**ectrosyndactyly** (ek"tro-sin-dak'tĭ-le) [Gr. *ektrōma* abortion + *syn* together + *daktylos* finger] a condition in which some of the digits are missing and those that remain are webbed, so that they are more or less attached.

**ectrotic** (ek-trot'ik) 1. pertaining to or producing abortion. 2. arresting the development of a disease.

**ectylurea** (ek"til-u-re'ah) chemical name: cis-(2-ethylcrotonyl)urea. A white crystalline powder, $C_7H_{12}N_2O_2$, used as a sedative.

**ectyonin** (ek"tĭ-on'in) an antimicrobial substance obtained from the sponge *Microciona prolifera*.

**ectype** (ek'tip) an unusual type of physical or mental constitution.

**ectypia** (ek-tĭ'pe-ah) deviation from type; the possession of an unusual type of constitution.

**eczema** (ek'zĕ-mah) [Gr. *ekzein* to boil out] 1. a superficial inflammatory process involving primarily the epidermis, characterized early by redness, itching, minute papules and vesicles, weeping, oozing, and crusting, and later by scaling, lichenification, and often pigmentation. It is not a disease entity or an acceptable diagnosis. 2. atopic dermatitis. **allergic e.** (*obs.*), allergic dermatitis. **atopic e.** (*obs.*), see under *dermatitis*. **e. cap'itis** (*obs.*), seborrheic dermatitis or allergic contact dermatitis of the scalp. **contact e.,** contact dermatitis (def. 1). **e. ep'ilans** (*obs.*), eczema with loss of hair. **e. epizoot'ica,** foot-and-mouth disease. **facial e. of ruminants,** a photosensitive disease of ruminants, particularly in New Zealand, due to ingestion of the spores of the mold *Pithomyces chartarum* (class Deuteromycetes), which contain sporidesmin. **flexural e.,** atopic dermatitis. **e. herpet'icum,** disseminated herpes simplex; see also *Kaposi's varicelliform eruption*. **impetiginous e.,** infectious eczematoid dermatitis. **infantile e.,** atopic dermatitis in infants. Called also *Besnier's prurigo (in Britain)*. **e. intertri'go,** intertrigo. **e. margina'tum,** tinea cruris. **nummular e., e. nummula're,** eczema in which the patches are coin shaped; it may be a form of neurodermatitis. **orbicular e.,** nummular e. **seborrheic e., e. seborrhoe'icum** (*obs.*), seborrheic dermatitis. **solar e., e. sola're** (*obs.*), polymorphous light eruption. **stasis e.,** stasis dermatitis. **e. vaccina'tum,** disseminated vaccinia; see also *Kaposi's varicelliform eruption*.

**eczematid, eczematide** (ek-zem'ah-tid) loosely, an eczematous lesion not caused by external contact-type allergy, or by infection in the involved area; the term has different uses in different countries and little currency in the United States.

**eczematization** (ek-zem"ah-ti-za'shun) persistent eczema-like lesions of the skin, usually due to the continued trauma of scratching.

**eczematogenic** (ek-zem"ah-to-jen'ik) causing eczema.

**eczematoid** (ek-zem'ah-toid) resembling eczema.

**eczematous** (ek-zem'ah-tus) affected with or of the nature of eczema.

**E.D.** erythema dose; effective dose.

**$E.D._{50}$** median effective dose; a dose that produces its effects in 50 per cent of a population.

**edathamil** (ĕ-dath'ah-mil) edetate.

**Eddowes' syndrome (disease)** (ed'ōz) [Alfred *Eddowes*, British physician, 1850–1946] see under *syndrome*.

**Edebohls' operation, position** (ed'e-bōlz) [George Michael *Edebohls*, New York surgeon, 1853–1908] see under *operation* and *position*.

**Edelman,** Gerald Maurice. American biochemist, born 1929, co-winner, with Rodney Porter, of the Nobel prize in physiology and medicine for 1972, for his work on the chemical structure of antibodies.

**Edelmann's anemia, cell** (a'del-manz) [Adolf *Edelmann*, physician in Vienna, 1885–1939] see under *anemia*, and see *kinetocyte*.

**edema** (ĕ-de'mah) [Gr. *oidēma* swelling] the presence of abnormally large amounts of fluid in the intercellular tissue spaces of the body; usually applied to demonstrable accumulation of excessive fluid in the subcutaneous tissues. **acute circumscribed e., acute essential e.,** angioneurotic e. **alimentary e.,** nutritional edema. **ambulant e.** (*obs.*), Calabar swelling; see under *swelling*. **angioneurotic e.,** a condition characterized by the sudden appearance of temporary edematous areas of the skin or mucous membranes and occasionally of the viscera, often associated with dermographia, urticaria, erythema, and purpura, which may be of allergic, neurotic, or of unknown origin. Called also *acute circumscribed e., Milton's e., Quincke's e., wandering e., giant urticaria*, etc. **angioneurotic e., hereditary,** a form similar to the nonhereditary form but tending to involve more visceral lesions, especially of the respiratory and gastrointestinal tracts. Two types, both autosomal dominant traits, are distinguished: one involves failure of synthesis of the inhibitor of complement component C1, the other involves the synthesis of an abnormal protein. **e. artefac'tum,** edema that is artificially produced. **Berlin's e.,** commotio retinae

**blue e.,** a puffed, bluish appearance of a limb in hysterical paralysis. **brain e.,** an excessive accumulation of fluid in the brain substance (*wet brain*); it may be due to various causes, including trauma, tumor, and increased permeability of the capillaries occurring as a result of anoxia or exposure to toxic substances. **brown e.,** hardening and infiltration of the lung with a brownish fluid. **e. bullo'sum vesi'cae,** a condition of the mucous lining of the bladder marked by the formation of clear vesicles with small white particles floating between them. **Calabar e.,** Calabar swellings. **e. cal'idum,** inflammatory e. **cardiac e.,** a manifestation of congestive heart failure, caused by increased venous and capillary pressures and often associated with the retention of sodium by the kidneys. **circumscribed e.,** angioneurotic e. **dependent e.,** edema affecting most seriously the lowermost or dependent parts of the body. **famine e.,** nutritional e. **fingerprint e.,** edema in which the whorls of the fingerprint are clearly visible after circumferential manipulation of a pressure point on the forehead or sternum, considered indicative of intracellular fluid excess. **e. frig'idum,** noninflammatory e. **e. fu'gax,** transient accumulation of fluid in a specific region. **gaseous e.,** edema accompanied with gas formation, as in gas bacillus infection and subcutaneous emphysema. **giant e.,** angioneurotic e. **hepatic e.,** edema due to faulty functioning of the liver. **high-altitude pulmonary e.,** pulmonary edema caused by hypoxia that develops as a result of prolonged exertion after ascending quickly to high altitudes without the benefit of acclimatization; seen especially in mountain climbers. **Huguenin's e.,** acute congestive edema of the brain. **hunger e.,** nutritional e. **hydremic e.,** edema in conditions marked by hydremia. **hysterical e.,** blue e. **idiopathic e.,** edema of unknown cause affecting women, occurring intermittently over a period of years and usually worse during the premenstrual phase; it is associated with increased aldosterone secretion. **inflammatory e.,** a form due to inflammation, and attended with redness and pain. **insulin e.,** edema which sometimes follows the injection of insulin. **invisible e.,** the accumulation of a considerable amount of fluid in the subcutaneous tissues before it becomes demonstrable. **local intracutaneous e.,** urticaria. **e. of lung,** pulmonary e. **lymphatic e.,** edema associated with obstruction of the lymph vessels. **malignant e.,** edema marked by rapid extension, with destruction of tissue and formation of a gas. **migratory e.,** angioneurotic e. **Milroy's e.,** see under *disease*. **Milton's e.,** angioneurotic e. **mucous e.,** myxedema. **e. neonato'rum,** a disease of premature and feeble infants that resembles sclerema and is marked by spreading edema with cold, livid skin. **nephrotic e.,** edema occurring in nephrosis and in the intermediate stage of diffuse nephritis. **neuropathic e.,** pseudolipoma. **noninflammatory e.,** edema without redness and pain, occurring from passive congestion or from lowered serum osmolarity. **nonpitting e.,** edema in which the tissues cannot be pitted by pressure. **nutritional e.,** a disorder of nutrition due to long-continued diet deficiency of protein and/or calories, and marked by anasarca and edema; called also *alimentary e.*, *famine e.*, *war e.*, *hunger e.*, and *nutritional, famine,* or *war dropsy*. **paroxysmal pulmonary e.,** pulmonary edema marked by nocturnal attacks of difficult respiration, audible rales, wheezes, and cough, caused by acute left ventricular failure, usually associated with hypertensive heart disease. **passive e.,** edema occurring because of obstuction to vascular or lymphatic drainage from the area. **periodic e.,** angioneurotic e. **periretinal e.,** central serous retinopathy. **Pirogoff's e.,** malignant e. **pitting e.,** edema in which the tissues show prolonged existence of the pits produced by pressure. **placental e.,** the presence of fluid in the villi of the placenta, the villi being club-shaped and irregularly swollen. **prehepatic e.,** edema occurring in prehepatic hypoproteinemia. **pulmonary e.,** abnormal, diffuse, extravascular accumulation of fluid in the pulmonary tissues and air spaces due to changes in hydrostatic forces in the capillaries or to increased capillary permeability; it is characterized clinically by intense dyspnea and, in the intra-alveolar form, by voluminous expectoration of frothy pink serous fluid and, if severe, by cyanosis. **purulent e.,** a swelling due to the effusion of a purulent fluid. **Quincke's e.,** angioneurotic e. **renal e.,** edema due to nephritis and the consequent hypoproteinemia. **rheumatismal e.,** painful red edematous swellings on the limbs in rheumatism, due to subcutaneous exudation. **salt e.,** edema produced by an increase of sodium chloride in the diet. **solid e.,** myxedema. **solid e. of lungs,** a rubbery consistency and gelatinous appearance of the lungs sometimes associated with hypertensive left ventricular failure and uremia. **terminal e.,** pulmonary edema which frequently develops as an agonal event from circulatory failure. **toxic e.,** edema caused by a poison. **venous e.,** edema in which the effused liquid comes from the blood. **vernal e. of lung,** edema of the lung occurring in spring and considered to be allergic. **wandering e.,** angioneurotic e. **war e.,** nutritional e.

**edematigenous** (ĕ-dem″ah-tij′ĕ-nus) edematogenic.

**edematization** (ĕ-dem″ah-tı-za′shun) the process of becoming or of making edematous.

**edematogenic** (ĕ-dem″ah-to-jen′ik) producing or causing edema.

**edematous** (ĕ-dem′ah-tus) pertaining to or affected by edema.

**Edentata** (e″den-ta′tah) an order of mammals including armadillos, tree sloths, and anteaters.

**edentate** (e-den′tāt) edentulous.

**edentia** (e-den′she-ah) [L. *e* without + *dens* tooth] absence of the teeth.

**edentulate** (e-den′tu-lāt) edentulous.

**edentulous** (e-den′tu-lus) [L. *e* without + *dens* tooth] without teeth; having lost the natural teeth.

**edetate** (ed′ĕ-tāt) ethylenediaminotetraacetate. Any salt of edetic acid; called also *edathamil*. Abbreviated EDTA. **e. calcium disodium, calcium disodium e.** [USP], chemical name: disodium [(ethylenedinitrilo)-tetraacetato]calciate(2-). A metal complexing agent, $C_{10}H_{12}CaN_2Na_2O_8 \cdot xH_2O$, consisting of a mixture of the dihydrate and trihydrate of calcium disodium ethylenediaminetetraacetate (predominantly the dihydrate), used in the diagnosis and treatment of lead poisoning. Called also *calcium edathamil* and *calciumedetate sodium*. **e. disodium or disodium e.** [USP], a white crystalline powder, $C_{10}H_{14}N_2Na_2O_8 \cdot H_2O$, freely soluble in water, used as a chelating agent in poisoning with lead and other heavy metals and, because of its affinity for calcium, in the treatment of hypercalcemia. Called also *edathamil disodium*. **e. sodium,** the sodium salt of ethylenediaminotetraacetate, a chelating agent. **e. trisodium,** the trisodium salt of ethylenediaminotetraacetate; a chelating agent.

**edge** (ej) a thin side or border. **cutting e.,** the angle formed by the merging of two flat surfaces, by which something may be cut, such as the blade of a knife, or the incisal surface of an anterior tooth. **denture e.,** see under *border*. **incisal e.,** the junction of the labial surface of an anterior tooth with a flattened linguoincisal surface created by occlusal wear.

**edge-strength** (ej′ strength) the resistance offered by an edge to a fracturing force, applied especially in dentistry to such resistance offered by the edge of an amalgam restoration.

**Edinger's law, nucleus** (ed′ing-gerz) [Ludwig *Edinger*, German neurologist, 1855–1918] see under *law* and *nucleus*.

**Edinger-Westphal nucleus** (ed′ing-ger-vest′fahl) [L. *Edinger*; Carl Friedrich Otto *Westphal*, German neurologist, 1833–1890] nucleus accessorius.

**edipism** (ed′ĭ-pizm) [from *Oedipus*, King of Thebes. See *Oedipus complex*] intentional injury of one's own eyes.

**Edlefsen's reagent test** (ed′lef-senz) [Gustav J. J. F. *Edlefsen*, German physician, 1842–1910] see under *reagent*.

**EDR** effective direct radiation; electrodermal response

**edrophonium chloride** (ed″ro-fo′ne-um) [USP] chemical name: (*m*-hydroxyphenyl) dimethylam-

apparently chemically identical with bilirubin but which has a different site of origin, being formed locally in the tissues from hemoglobin, particularly under conditions of reduced oxygen tension.

**hematokolpos** (hem″ah-to-kol′pos) hematocolpos.

**hematokrit** (he-mat′o-krit) hematocrit.

**hematolin** (hem″ah-to′lin) a compound, $C_{68}H_{78}O_7N_8$, from heme.

**hematolith** (hem′ah-to-lith) (*obs.*) hemolith.

**hematologist** (hem″ah-tol′o-jist) a specialist in the study of the blood.

**hematology** (hem″ah-tol′o-je) [*hemato-* + *-logy*] that branch of medical science which treats of the morphology of the blood and blood-forming tissues.

**hematolymphangioma** (hem″ah-to-lim″fan-je-o′mah) [*hemato-* + L. *lympha* lymph + Gr. *angeion* vessel] + *-oma*] a tumor composed of blood vessels and lymph vessels.

**hematolysis** (hem″ah-tol′i-sis) hemolysis.

**hematolytic** (hem″ah-to-lit′ik) hemolytic.

**hematoma** (hem″ah-to′mah), pl. *hemato′mas* [*hemato-* + *-oma*] a localized collection of blood, usually clotted, in an organ, space, or tissue, due to a break in the wall of a blood vessel. **aneurysmal h.,** false aneurysm. **h. au′ris,** hematoma of the perichondrium of the ear. **epidural h.,** accumulation of blood in the epidural space, due to damage to the middle meningeal artery and producing compression of the dura mater and thus compression of the brain. Unless evacuated, it may result in herniation through the tentorium, and death. **pelvic h.,** a collection of blood in the pelvic cellular tissue. **perianal h.,** a hematoma under the perianal skin, caused by rupture of a subcutaneous vessel, the blood being kept localized by fibroelastic septa and causing much pain. **retrouterine h.,** an effusion of blood into the retrouterine connective tissue. **subdural h.,** accumulation of blood in the subdural space. In the severe *acute* form, both blood and cerebrospinal fluid enter the space as a result of laceration of the brain and a tear in the arachnoid, adding subdural compression to the direct injury to the brain. In the *chronic* form, only blood effuses into the subdural space as a result of rupture of the bridging veins, usually due to closed head injury. The effusion is a gradual process resulting, weeks after the injury, in headache, progressive stupor, and hemiparesis, followed by dilating pupil, a sign of herniation of the tentorium. **subungual h.,** an accumulation of blood under the nail plate.

**hematomancy** (hem′ah-to-man-se) [*hemato-* + Gr. *manteia* divination] diagnosis by examination of the blood.

**hematomanometer** (hem″ah-to-mah-nom′ĕter) sphygmomanometer.

**hematomediastinum** (hem″ah-to-me″de-as-ti′num) [*hemato-* + *mediastinum*] hemomediastinum.

**hematometakinesis** (hem″ah-to-met″ah-ki-ne′sis) [*hemato-* + Gr. *meta* across + *kinesis* movement] the phenomenon of the shifting of blood from one part of the body to another, as from the skin to the internal organs; called also *borrowing-lending hemodynamic phenomenon*.

**hematometer** (hem″ah-tom′ĕ-ter) [*hemato-* + Gr. *metron* measure] a hemoglobinometer.

**hematometra** (hem″ah-to-me′trah) [*hemato-* + Gr. *mētra* uterus] an accumulation of blood in the uterus.

**hematometry** (hem″ah-tom′e-tre) [*hemato-* + Gr. *metron* measure] measurement of the hemoglobin and estimation of the percentage of the various cells in the blood.

**hematomole** (he-mat′o-mōl) Breus' mole.

**hematomphalocele** (hem″at-om-fal′o-sēl) [*hemat-* + *omphalocele*] an umbilical hernia containing blood.

**hematomphalus** (hem″at-om′fah-lus) Cullen's sign; see under *sign*.

**hematomycosis** (hem″ah-to-mi-ko′sis) (*obs.*) fungemia.

**hematomyelia** (hem″ah-to-mi-e′le-ah) [*hemato-* + Gr. *myelos* marrow + *-ia*] hemorrhage into the spinal cord, usually confined to the gray substance, most often due to trauma, and marked by the sudden onset of flaccid paralysis with sensory disturbances.

**hematomyelitis** (hem″ah-to-mi″ĕ-li′tis) [*hemato-* + *myelitis*] acute myelitis with bloody effusion within the spinal cord.

**hematomyelopore** (hem″ah-to-mi′el-o-pōr″) [*hemato-* + Gr. *myelos* marrow + *poros* opening] a disease marked by the formation of canals in the spinal cord, due to hemorrhage.

**hematoncometry** (hem″at-on-kom′ĕ-tre) [*hemat-* + Gr. *onkos* mass + *metron* measure] measurement of blood volume.

**hematonephrosis** (hem″ah-to-nĕ-fro′sis) presence of blood in the pelvis of the kidney.

**hematonic** (hem″ah-ton′ik) a blood tonic.

**hematonosis** (hem″ah-ton′o-sis) any disease of the blood.

**hematopathology** (hem″ah-to-pah-thol′o-je) hemopathology.

**hematopedesis** (hem″ah-to-pĕ-de′sis) hemodiapedesis.

**hematopenia** (hem″ah-to-pe′ne-ah) [*hemato-* + Gr. *penia* poverty] deficiency of blood.

**hematopericardium** (hem″ah-to-per″i-kar′de-um) hemopericardium.

**hematoperitoneum** (hem″ah-to-per″i-to-ne′um) hemoperitoneum.

**hematopexin** (hem″ah-to-pek′sin) hemopexin.

**hematopexis** (hem″ah-to-pek′sis) hemopexis.

**hematophage** (hem′ah-to-faj) hemophagocyte.

**hematophagia** (hem″ah-to-fa′je-ah) 1. blood drinking. 2. the act of subsisting on the blood of another animal. 3. hemocytophagia.

**hematophagocyte** (hem″ah-to-fag′o-sit) hemophagocyte.

**hematophagous** (hem″ah-tof′ah-gus) [*hemato-* + Gr. *phagein* to eat] pertaining to or characterized by hematophagia.

**hematophagy** (hem″ah-tof′ah-je) hematophagia.

**hematophilia** (hem″ah-to-fil′e-ah) hemophilia.

**hematophyte** (hem′ah-to-fit″) [*hemato-* + Gr. *phyton* plant] (*obs.*) any vegetable microorganism or species living in the blood.

**hematophytic** (hem″ah-to-fit′ik) (*obs.*) pertaining to or caused by hematophytes.

**hematopiesis** (hem″ah-to-pi′ĕ-sis) [*hemato-* + Gr. *piesis* pressure] blood pressure.

**hematoplasmopathy** (hem″ah-to-plaz-mop′ah-the) [*hemato-* + *plasma* + Gr. *pathos* disease] any disorder due to alteration of the protein constitution of the blood.

**hematoplast** (hem′ah-to-plast) hemocytoblast.

**hematoplastic** (hem″ah-to-plas′tik) [*hemato-* + Gr. *plassein* to mold] concerned in the elaboration of the blood.

**hematopoiesis** (hem″ah-to-poi-e′sis) [*hemato-* + Gr. *poiein* to make] the formation and development of blood cells. **extramedullary h.,** the formation and development of blood cells outside the bone marrow, as in the spleen, liver, and lymph nodes.

**hematopoietic** (hem″ah-to-poi-et′ik) [*hemato-* + Gr. *poiein* to make] 1. pertaining to or affecting the formation of blood cells. 2. an agent that promotes the formation of blood cells.

**hematopoietin** (hem″ah-to-poi′e-tin) erythropoietin.

**hematoporphyria** (hem″ah-to-por-fi′re-ah) porphyria.

**hematoporphyrin** (hem″ah-to-por′fi-rin) [*hemato-* + Gr. *porphyra* purple] chemical name: 1,3,5,8-tetramethyl-2,4-bis(α-hydroxyethyl)-6,7-dipropionic acid porphin. A dark violet, iron-free powder resulting from decomposition of hemoglobin, with the addition of HOH to the vinyl groups.

**hematoporphyrinemia** (hem″ah-to-por-fi-rin-e′me-ah) the presence of hematoporphyrin in the blood.

**hematoporphyrinism** (hem″ah-to-por′fi-rin-izm) a state characterized by hematoporphyrinemia and a sensitiveness to sunlight.